

Appl. No. : 10/725,962
Filed : December 2, 2003

AMENDMENTS TO THE SPECIFICATION

Please replace paragraphs [0071], [0072], [0085], [0086], [0087], [0108], [0109], [0111], [0112], and [0113] with the corresponding rewritten paragraphs below:

-- [0071] One method for generating fully human antibodies is through the use of ~~XenoMouse~~TM XENOMOUSE[®] strains of mice which have been engineered to contain 245 kb and 190 kb-sized germline configuration fragments of the human heavy chain locus and kappa light chain locus. See Green et al. Nature Genetics 7:13-21 (1994). The ~~XenoMouse~~ XENOMOUSE[®] strains are available from Abgenix, Inc. (Fremont, Calif.). --

-- [0072] The production of the ~~XenoMouse~~ XENOMOUSE[®] strains of mice is further discussed and delineated in U.S. patent application Ser. No. 07/466,008, filed Jan. 12, 1990, Ser. No. 07/610,515, filed Nov. 8, 1990, Ser. No. 07/919,297, filed Jul. 24, 1992, Ser. No. 07/922,649, filed Jul. 30, 1992, filed No. 08/031,801, filed Mar. 15, 1993, Ser. No. 08/112,848, filed Aug. 27, 1993, Ser. No. 08/234,145, filed Apr. 28, 1994, Ser. No. 08/376,279, filed Jan. 20, 1995, Ser. No. 08/430, 938, Apr. 27, 1995, Ser. No. 08/464,584, filed Jun. 5, 1995, Ser. No. 08/464,582, filed Jun. 5, 1995, Ser. No. 08/463,191, filed Jun. 5, 1995, Ser. No. 08/462,837, filed Jun. 5, 1995, Ser. No. 08/486,853, filed Jun. 5, 1995, Ser. No. 08/486,857, filed Jun. 5, 1995, Ser. No. 08/486,859, filed Jun. 5, 1995, Ser. No. 08/462,513, filed Jun. 5, 1995, Ser. No. 08/724,752, filed Oct. 2, 1996, and Ser. No. 08/759,620, filed Dec. 3, 1996 and U.S. Pat. Nos. 6,162,963, 6,150,584, 6,114,598, 6,075,181, and 5,939,598 and Japanese Patent Nos. 3 068 180 B2, 3 068 506 B2, and 3 068 507 B2. See also Mendez et al. Nature Genetics 15:146-156 (1997) and Green and Jakobovits J. Exp. Med. 188:483-495 (1998). See also European Patent No., EP 0 463 151 B1, grant published Jun. 12, 1996, International Patent Application No., WO 94/02602, published Feb. 3, 1994, International Patent Application No., WO 96/34096, published Oct. 31, 1996, WO 98/24893, published Jun. 11, 1998, WO 00/76310, published Dec. 21, 2000. The disclosures of each of the above-cited patents, applications, and references are hereby incorporated by reference in their entirety. --

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-- [0085] Antibodies in accordance with the invention were prepared through the utilization of the ~~XenoMouse~~ XENOMOUSE® strains of mice technology, as described below. Such mice, then, are capable of producing human immunoglobulin molecules and antibodies and are deficient in the production of murine immunoglobulin molecules and antibodies. Technologies utilized for achieving the same are disclosed in the patents, applications, and references disclosed in the Background, herein. In particular, however, a preferred embodiment of transgenic production of mice and antibodies therefrom is disclosed in U.S. patent application Ser. No. 08/759,620, filed Dec. 3, 1996 and International Patent Application Nos. WO 98/24893, published Jun. 11, 1998 and WO 00/76310, published Dec. 21, 2000, the disclosures of which are hereby incorporated by reference. See also Mendez et al. Nature Genetics **15**:146-156 (1997), the disclosure of which is hereby incorporated by reference. --

-- [0086] Through use of such technology, we have produced fully human monoclonal antibodies to a variety of antigens. Essentially, we immunize ~~XenoMouse~~TM XENOMOUSE® lines of mice with an antigen of interest, recover lymphatic cells (such as B-cells) from the mice that expressed antibodies, and fuse such recovered cell lines with a myeloid-type cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produced antibodies specific to the antigen of interest. Herein, we describe the production of multiple hybridoma cell lines that produce antibodies specific to drugs of abuse. Specific examples disclosed herein include antibodies specific to amphetamine, methamphetamine, and phencyclidine. Further, we provide a characterization of the antibodies produced by such cell lines, including nucleotide and amino acid sequence analyses of the heavy and light chains of such antibodies. --

-- [0087] Alternatively, instead of being fused to myeloma cells to generate hybridomas, the recovered cells, isolated from immunized ~~XenoMouse~~TM XENOMOUSE® lines of mice, are screened further for reactivity against the initial antigen, preferably amphetamine, methamphetamine, or phencyclidine. --

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-- [0108] Drug haptens were employed as an immunogen to stimulate an immune response in ~~Xenomouse~~[®] XENOMOUSE[®] strains of animals (Abgenix Inc, Fremont, Calif.). Specifically, the drugs against which the antibodies were raised were amphetamine, methamphetamine, and phencyclidine. Monoclonal antibodies directed against the drugs of abuse were prepared by hybridoma technology from immunized Xenomouse animals in standard fashion. --

-- [0109] Table 5 shows an immunization schedule in which mice were immunized with the various immunoconjugates. UA001 refers to an immunoconjugate of a methamphetamine hapten bound to BSA, UA002 refers to an immunoconjugate of an amphetamine hapten bound to BSA, UA003 refers to an immunoconjugate of a phencyclidine (PCP) hapten bound to BSA. For each immunoconjugate, two groups of mice were used; group 1 contained ~~Xenomouse~~ XENOMOUSE[®] xmg2 strain mice (Abgenix, Inc., Fremont Calif.) while group 2 contained ~~Xenomouse~~ XENOMOUSE[®] 3C-1 strain mice (Abgenix, Inc., Fremont Calif.). --

-- [0111] Table 7 shows titer data illustrating the ~~Xenomouse~~ XENOMOUSE[®] strains of mice response in group 1 to the ~~innoculation~~ inoculation with the amphetamine-BSA immunoconjugate. The mouse ID numbers are shown in the left ~~column~~ column; NC(h) refers to a negative control (human), NC(m) refers to negative control (mouse), and PC(m) refers to positive control (mouse). --

-- [0112] Table 8 shows titer data illustrating the ~~Xenomouse~~ XENOMOUSE[®] strains of mice response in group 2 to the ~~innoculation~~ inoculation with the amphetamine-BSA immunoconjugate. The mouse ID numbers are shown in the left ~~column~~ column; NC(h) refers to a negative control (human), NC(m) refers to negative control (mouse), and PC(m) refers to positive control (mouse). --

-- [0113] Table 9 shows titer data illustrating the ~~Xenomouse~~ XENOMOUSE[®] strains of mice response in group 3 to the ~~innoculation~~ inoculation with the AMP(+)MO6-KLH immunoconjugate. The mouse ID numbers are shown in the left ~~column~~ column; NC refers to a negative control and PC refers to a positive control. --